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THE HIPPOCAMPUS AND THE ORIENTING REFLEX

UNPUBLISHED PRELIMINARY DATA

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Abstract

Electrical activity in the cat's hippocampus has been studied in alerted but non-performing animals, and in the course of discriminative task performances, and during orienting behavior. Computed averages of hippocampal wave trains were prepared of daily trials in discrimination and in orienting responses. Alerted but non-performing animals exhibited a wide spectrum of "theta" wave activity in the range 3 to 7 cycles/sec on first introduction into the test situation, without overt aspects of orienting behavior. This activity persisted in EEG epochs between discriminative and orienting trials throughout many months of training. It was maximal in leads from the pyramidal cell dendritic layer. By contrast, leads in basal parts of the dentate gyrus and subiculum were characterized by "fast, low-voltage" activity in the alerted animal. During T-maze discriminative performances hippocampal theta waves regularized at 6 cycles/sec, and also replaced the low voltage fast activity in the zones cited above. Orienting behavior was associated with slower and less regular computed averages at 4 to 5 cycles/sec. Single doses of LSD-25 were followed by prolonged disinhibition of inhibited orienting behavior, and by the gradual appearance of a regular EEG average during orientations 5 to 10 days after the drug, and declining after 15 to 20 days, concurrently with the decline of orienting behavior. A similar but accelerated series of behavioral and EEG changes was induced by a psychotomimetic cyclohexamine, CL-400. It is concluded that within a single brain system, there is a clear capacity for participation in related but differing behavioral responses, with induction of greatly differing EEG patterns in discriminative and orienting responses. The possible relation of these wave patterns to the establishment of a behavioral "set," necessary to storage or recall of information is discussed.

Introduction

It is characteristic of virtually all living organisms, from the unicellular ameba to man himself, that introduction of novel environmental stimuli produces an alerting response. This response varies in its behavioral manifestations, depending on the level of neural organization of the particular species, and the nature and intensity of the stimulus. In the mammal, the response to a sudden stimulus runs a gamut from the "startle response," with arrest of ongoing behavior, through various investigative reactions, to an almost infinite variety of complex, coordinated motor patterns, constituting "fight or flight" responses (10). It is in the second category that we may group the behavioral components of the orienting reflex. First described by Pavlov (13) as "the reflex that brings about the immediate response in man and animals, so that they immediately orient their appropriate receptor-organ in accordance with the perceptible quality in the agent bringing about the change, making full investigation of it," orienting behavior has been characterized by Konorski (17) in terms of its most salient feature, the turning of head and eyes towards the novel stimulus. Recent reviews by Sokolov (20) and Vinogradova (21) have emphasized that its characteristic motor, vascular and EEG reactions can appear not only as components of the orienting reflex, but also as components of other unconditioned reflexes. The uniqueness of the orienting reflex therefore rests on certain "principles" in the intimate behavior of its component reflexes, including their non-specificity with respect to both quality and intensity of the stimulus, and the selectivity of extinction of various properties of the stimulus with repeated presentation.

Attempts to find electrophysiological correlates of the orienting reflex led Grastyan and his colleagues (1959, 1960) to postulate a specific relationship between hippocampal theta wave trains and orienting behavior. However, the exquisite plasticity of hippocampal theta rhythms in changing behavioral states, including the appearance of bursts of waves in a narrow spectral range during performance of a visual discriminative task, have suggested more subtle and specific relationships to discriminative functions and judgment capability (1, 3, 5, 7-9). For these reasons, discussed in further detail below, we have attempted in this study to distinguish hippocampal theta trains accompanying discriminative performances from those trains with widely swinging spectral content occurring in alerted states, including orienting behavior.

Methods

Five adult cats (body weights 2.8 to 4.0 kg) were stereotaxically implanted with bilateral arrays of dorsal hippocampal electrodes. Each array was formed of six 34 gauge stainless steel wires, insulated with enamel and epoxy varnish, and spaced 1.5 mm apart (19). In three animals, these arrays were disposed transversely in the dorsal hippocampus, and in the remaining two were inclined obliquely to the sagittal plane to follow the long axes of the divergent posterior portions of the dorsal hippocampi. The relative lengths of the wires in each array were carefully trimmed to follow the contour of the dendritic zone of the hippocampal pyramidal cell layer. Bipolar EEG recordings were made from adjacent pairs of wires in each array, using an 8 channel Grass electroencephalograph.

Behavioral Training. This involved a modification of the T-maze procedure used extensively in previous studies (3, 5, 9). The subject was required to make an initial direct approach to the lighted side of the T-box to secure a concealed food reward. Opening of the doors in the start box was reinforced by a 500 cycles/sec tone that persisted for the duration of the trial. Forty approach trials were presented daily. In addition, 40 "orienting" trials were randomly interspersed between the approach trials. In these orienting trials, the doors of the start box remained closed, but the subject was able to hear the reinforcing tone, and observe the ambient illumination in the reward area from the cue light, through narrow slots above and below the opaque starting doors. In three subjects, the orienting trials were introduced at the commencement of training. In the other two, they were withheld until a high level (over 90 per cent) was reached in approach performance.

Drug Studies. Psychotropic agents were administered in single intraperitoneal doses at intervals of not less than 21 days. Freshly prepared aqueous solutions of lysergic acid diethylamide (LSD-25) were given in doses of 70 to 90 μg/Kg. Doses of n-ethyl-1-phenyl cyclohexylamine monohydrochloride (CL-400) were given in amounts of 2.0 mg/Kg, prepared by a five-fold dilution of a commercial preparation. Early effects of the drug were assessed by comparison of 20 pre-drug trials with the same number presented 45 to 60 min after injection.

Computer Analysis of EEG Records. Averaging of hippocampal wave trains was performed on-line with a Mnemotron CAT. A series of pulse generators (Grass Model IV stimulators) provided pulse trains for initiation of computer analysis epochs and for gating visual and auditory cues. A 2.0 sec analysis epoch was arranged to begin 250 to 500 msec before presentation of the task.

Histological Controls. After formalin fixation serial frozen sections were cut in the long axis of the arrays, and the hippocampal location of those dipoles used in the computational analysis confirmed.

Results

Particular care was taken in observing the characteristics of theta trains occurring in initial exposure in the test box. Our previous findings were fully confirmed that high amplitude, slow wave trains are fully developed from the initial moments of the exposure, and are not dependent on the initiation of specific aspects of orientation (5, 19). In contrast to the narrow bandwidth of the trains accompanying the discriminative performance, this continuous background of theta activity covered about an octave from 3 to 7 cycles/sec. It was little changed between the commencement and termination of a day's training, so that at least partial satiation of hunger was not an influential factor; nor did it decline progressively during several months of daily training. Its ubiquitous incidence as a broad spectrum is interpreted as relating to a state of alertness, without orienting or discriminative responses as an essential concomitant.

These findings are exemplified in Fig. 1. In the pre-approach epochs of control records, and particularly in right hippocampal leads (R. HIPP., 12-13, 13-14), high amplitude slow waves occurred at this time, with frequencies ranging from 4 to 7 cycles/sec. They contrasted sharply with the burst of more regular waves at 6 cycles/sec appearing during the discriminative approach to food, also most obvious in this example in a right hippocampal lead (13-14). Detection of this phenomenon in its fullest extent is critically dependent on the location of the recording electrodes, histologically confirmed in this instance as lying in the deeper part of the pyramidal cell layer in zone CA3. It will also be noted that this regular burst of waves, lasting approximately two seconds in approach trials preceding (A) and one day after drug treatment (B), subsided rapidly on attainment of the food reward. Further evaluation by computer analysis is described below.

1. <u>Effects of introduction of orienting trials in schedules of trained animals</u>.

Introduction of orienting trials, as described in Methods, in animals already at a high performance level was accompanied by substantial orienting responses, including turning of head and trunk towards the starting doors, and in some instances by initiation of walking. These orienting movements subsided and essentially disappeared in the course of 7 to 10 days' training.

Typical concomitant electrophysiological events are shown in Fig. 2. These computed results depict the sharply contrasting regularity of the daily average during approach, extending throughout the 2.0 second analysis period on many days (A), by comparison with averages of an equal number of orienting trials (B). The former were characterized by an initial burst of 4 or 5 waves of substantially higher amplitude than those in the latter part of the approach. The latter showed only low amplitude irregular waves at the onset of the orienting situation in the first six days' training. Moreover, dominant frequencies in orienting trials varied widely within and between daily averages, ranging between 4 and 5 cycles/sec, substantially slower than wave trains from the same lead during approach.

The most regular portions of the orienting averages tended to lie towards their terminations. A trend towards higher amplitude initial waves was noted in the orienting averages of days 9, 10 and 11.

2. <u>Prolonged effects of LSD on orienting behavior and hippocampal EEG.</u>

The prolonged effects of LSD on the hippocampal theta wave trains during a discriminative performance have been described in detail elsewhere (6). Typically (Fig. 3A), there was an enhancement of the amplitude and regularity of the initial waves of the approach train, beginning 3 or 4 days after a dose of 80 μg/Kg and persisting for 5 to 7 days thereafter. It should be emphasized that such a dose, though large by comparison with threshold doses in other mammals, including man, was found to be the lowest dose capable of consistently inducing episodic electrical paroxysms in the cat in a well-lit environment. Furthermore, disruption of learned performance at this dose was slight (3).

Attention was directed in this study to persistent changes in orienting behavior induced by such a single dose of LSD. In Pavlovian terminology, this involved a disinhibition of the inhibited orienting reflex. The animal showed a renewal of the head and body turning, and associated searching movements that had characterized the initial exposure to the orienting trials. In this case, however, the orienting responses persisted for about 20 days after a single dose of LSD.

In the first 2 or 3 days after LSD, the orienting averages exhibited no consistent changes (Fig. 3B). This animal had received one previous dose of LSD 24 days earlier. Progressively, however, there was a trend towards higher amplitudes in the initial waves of the train, clearly manifested after 8 to 10 days. Between the eleventh and twenty-first days

(3/14/64 to 3/24/64), this initial regular train evolved into a sequence of 3 or 4 waves at 5 cycles/sec only slightly slower than those in the accompanying discriminative performances, and followed by a regular train of lower amplitude waves at the same frequency. This regularization of the orienting average declined thereafter with the habituation of the orienting behavior.

It will be noted that in this animal, the increment in the discriminative averages after LSD (Fig. 3A) occurred between the third and tenth days after the drug, in agreement with previous findings (6). It thus essentially preceded the development of the more rhythmic characteristics in the orienting averages. In other animals of this series, a similar dissociation was also seen. The effects of LSD in incrementing the discriminative average sometimes appeared on the first and second days after the drug, persisting for about 5 days (Fig. 4B), with dominant frequencies at about 6.5 cycles/sec. The orienting averages here manifested increasing regularity from the fifth day after the drug (3/16/64), declining after the fifteenth day. Their dominant frequencies were at about 5 cycles/sec, markedly slower than in the discriminative averages.

3. <u>Prolonged effects of a psychotomimetic cyclohexamine (CL-400) on orienting behavior and hippocampal EEG</u>.

The induction of paroxysmal seizure-like hippocampal wave trains in the cat with this series of drugs (Fig. 4) has been discussed in detail elsewhere (4). Our previous findings were confirmed, including the disruption of normal hippocampal theta wave trains, and the susceptibility of hippocampal tissue to these paroxysmal discharges in response to sudden auditory and visual stimuli. In the dose given (2 mg/Kg I.P.), behavioral performance and concomitant EEG activity were profoundly disrupted in 10 to 20 min. After 24 hours, occasional paroxysms were noted, with disruption of learned performance during these episodes.

On the first two days after the drug, there was characteristically a marked increase in orienting responses, and some augmentation in amplitude and regularity of hippocampal activity in the waiting periods (Fig. 1). The sustained regularity of theta wave trains during discriminative performances in post-drug trials was sharply augmented (Fig. 1B). Computed averages (Fig. 5), showed increased regularity throughout the 2.0 second analysis epoch in both discriminative and orienting responses for three days after the drug, but this was less sustained thereafter. This decline corresponded with diminished orienting behavior, which was more ephemoral after CL-400 than with LSD. As noted above, the dominant frequency in the discriminative responses was 6.5 cycles/sec, and in the orienting responses 5 cycles/sec. A similar transient augmentation in the regularity of the computed averages in orienting responses is shown in Fig. 6B (4/1/64 and 4/2/64).

Discussion

In his comprehensive review of the orienting reflex, Sokolov (1963) has drawn attention to three features regarded as characteristic; non-specificity with respect to quality of stimulus, non-specificity with regard to intensity, and selectivity of extinction of various properties of the stimulus with repeated presentations. In this study, our attention has been primarily directed to those classical aspects of orientation which most authors have regarded as somatic components of the reflex, involving turning of head and eyes towards a stimulus complex.

The frame of reference offered by Sokolov emphasized non-specificity of EEG responses accompanying a wide repertoire of specific reflexes in different species, citing the studies of Galambos (12), John (16) and Voronin (22). The present study indicates, on the contrary, that in the cat, at least, it is necessary to take account of hippocampal wave trains with characteristic features that relate in clear and specifiable ways to the performance of a discriminative task, and in different, but equally recognizable patterns, to aspects of orienting behavior.

The occurrence of hippocampal theta wave trains within a narrow frequency band around 6 cycles/sec during discrimination with visual cues has been described elsewhere (5, 15, 19). Temporary disruption of these wave trains by lesions remotely located in subthalamic zones of the diencephalon was associated with loss of discriminative capability, but was without effect on classical motor responses occurring as initial components of the discriminative performance (9). There is thus little support for the view that EEG reactions in a repertoire of conditional reflexes are quite similar.

Indeed, the present study has emphasized that characteristic patterns of theta waves, phase locked in computed averages to the moment of presentation of the discriminative task, persist into substantial degrees of overtraining. On the other hand, less regular and slower wave trains accompanying the orienting performance remained at a low level with habituation of orienting behavior. Further dissection of the inter-relations and differences between EEG concomitants of discriminative and orienting behavior has been possible in the late changes induced by LSD-25 and a cyclohexamine drug (CL-400). Following both drugs, there was enhanced orienting behavior and the regularization of concomitant theta wave trains. The time course of behavioral changes was slower in onset and longer lasting with LSD than with CL-400. In both cases, there was a good correlation between exaggeration of orienting behavior and the enhancement of rhythmic computed EEG averages. The gradual evolution of a rhythmic daily average in orienting responses after a single dose of LSD occurred with a striking independence of the faster, more regular averages of discriminative trials with which they were interspersed (Fig. 3). There is thus within a single brain system a clear capacity for participation in related but differing behavioral responses, with each of the two behavioral patterns characterized by greatly differing EEG patterns.

If, then, it is possible to relate such patterned hippocampal EEG activity to finer shades of behavioral responsiveness, it is necessary to consider the gamut of changing spectral content in these wave trains, and their possible relationship to broader states of alertness and focused attention. Grastyan (13) and Grastyan et al. (14) have described a hippocampal response to unfamiliar stimuli characterized by desynchronization and disappearance of slow waves. This phenomenon was without a behavioral manifestation, and was replaced by a slow wave burst only after these indifferent stimuli had achieved conditional significance, and were accompanied by the gradual development of orienting behavior. On the other hand, our studies here and those cited above have clearly indicated that the mere aspect of an alerted state, without either gross orienting behavior or the imposition of a discriminative performance, was uniformly accompanied by a rich gamut of hippocampal slow waves. These waves were present, particularly in leads primarily located in the dendritic zone of the pyramidal cell, from the first moments of exposure to the test situation, and thus do not support the view that the waves arise secondarily to the development of an orienting reflex.

A possible solution to these seemingly incompatible findings may lie in the recent evaluation of regional distribution of theta wave trains in alerted states and discriminative performances. Bipolar records from transverse arrays of chronically implanted electrodes in the cat's dorsal hippocampus (Porter, Adey and Brown, 1964, Fig. 6) clearly showed that remarkable regional differences exist, particularly in simultaneous records during alerted epochs between successive discriminative performances. They have indicated that deeper regions of the dentate fascia, and the subiculum, for example, may have a "fast desynchronized" activity in inter-trial epochs. Hippocampal dendritic zones, however, simultaneously showed a spectrum of high amplitude theta waves. Nevertheless, leads exhibiting much fast activity during intertrial epochs typically showed the 6 cycles/sec burst during discrimination, and also frequently showed a 4 to 5 cycles/sec train during orientation (Fig. 1, trial 24, 5-6, 12-13). It would thus seem necessary to take more critical account than has been customary of precise anatomical locations within the hippocampus in seeking behavioral correlates of its rhythmic processes.

Our current understanding of the role of hippocampal structures in memory and learning has recently been comprehensively reviewed by Drachman and Ommaya (11), who have examined this problem in the frame of three types of defects: loss of retention, or retrograde memory loss; impairment of acquisition, or inability to learn; and short-term or recent memory loss. They have concluded that medial temporal lobe damage is associated in man and animals with loss of retention and impairment of acquisition, rather than with impaired short-term memory.

Their findings thus direct attention to the participation by hippocampal structures in those processes of focused attention necessary to the acquisition and storage of information. Certainly, they do not support notions of the hippocampus as the actual site of the memory trace. The present study has exemplified the exquisite sensitivity of neuroelectric processes in the hippocampus to subtle shifts in cerebral states associated with either discriminative or orienting responses. Our previous studies (2, 7, 3) have indicated ways in which the hippocampal theta activity during discrimination has the characterisics of a "pace-maker," and how fragmentary, less regular aspects of these rhythms can be discerned simultaneously in subcortical structures, such as the midbrain reticular formation and the subthalamus, and in primary sensory pathways, including sensorimotor and visual cortex. It has been suggested that the deposition of a "memory trace" in extrahippocampal systems may depend on such wave trains, and subsequent recall on the stochastic reestablishment of similar wave patterns (7). Our findings here support the view that these electrical wave patterns are indeed the concomitants of the establishment of a behavioral "set," necessary to the storage or recall of information. In this notion of hippocampal activity, then, we may speculate on the significance of its continuous but ceaselessly varying wave processes, as they might underlie that most fascinating continuum in consciousness leading from the immediate past through the present to the immediate future. It is this aspect of a continuum in the temporal domain that may afford us clues to experimental analysis of hippocampal-subcortical relations that underlie acquisition and storage of information.

Footnotes

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Legends to Figures

Fig. 1. Typical EEG records in control records and after CL-400 during T-maze discriminative responses (left tracings) and orienting responses (right tracings). After the drug, the regularity of 6 cycles/sec activity was enhanced during discrimination, and in orienting responses, slower wave trains were also enhanced. The vertical barline indicates moment of behavioral presentation, including onset of 500 cycles/sec tone.

Fig. 2. Effects of introduction of orienting trials (daily n = 40) into training schedules of cat already at high level in discriminative task performance. Computed averages during discrimination (A) showed high amplitude waves at 6 cycles/sec. Randomly interspersed orienting trials (B) exhibited a lower amplitude 4 to 5 cycles/sec rhythm in later parts of analysis epoch.

Fig. 3. Effects of a single dose of LSD on hippocampal EEG in same animal as in Fig. 2, with typical augmentation of discriminative averages from third to tenth day after drug (A). In similar averages of orienting responses (B), a more regular average appeared about the tenth day (3/14/64), and persisted for approximately 10 days.

Fig. 4. Brief paroxysms of high amplitude slow waves and wave-and-spike discharges appearing 1 hour after CL-400 (2 mg/Kg I.P.).

Fig. 5. Increased regularity in computed averages of both discriminative and orienting responses for 3 days after CL-400 (2 mg/Kg).

Fig. 6. Transient augmentation in the regularity of the computed averages in orienting responses (B) on second and third days after CL-400 (2 mg/Kg).